REMARKS

Favorable reconsideration is respectfully requested in view of the foregoing amendments and the following remarks.

Claims 1-5, 7, 11, 13-17 and 19 are pending and claims 1-5 and 7 were rejected. Claims 11, 13-17 and 19 are withdrawn as non-elected subject matter.

In item 4 on pages 2-5 of the Office Action, claims 1-5 and 7 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Chenchik et al. (US 5,962,271) in view of Brennan et al. (Methods in Enzymology, 1983). Also, on pages 5-10, claims 1-5 and 7 were rejected under 35 U.S.C. § 103(a) as being unpatentable over Okayama et al. (Molecular and Cellular Biology, 1982) in view of Brennan.

Applicants respectfully traverse these rejections.

The main issue of this invention with regard to patentability is whether Brennan teaches a step (iii) of claim 1, i.e., "circularizing the mRNA/cDNA heteroduplex by ligating the 3' end of the first strand cDNA to the 5' end of the first strand of the double stranded DNA promer using T4 RNA ligase to form a circular mRNA/cDNA heteroduplex".

In response to Applicant's arguments, the Examiner states, *while the art and Brennan has established that T4 RNA ligase is not a preferred option for ligating DNA, it does not exclude the fact that T4 RNA ligase can be use to ligate DNA to DNA. Brennan clearly establishes this fact in the teaching short DNA oligomers* can *be both circularized and joined intermolecularly (page 39). The sentence noted by Applicant in Brennan et al does not establish that double stranded DNA is incapable of being circularized by an* RNA *ligase, rather* it *only established a DNA oligomer (which can be double stranded) and single stranded DNA oligomer (instead of a double stranded DNA oligomer) can be joined in good yield. DNA oligomer without reference to* it *being "single stranded" is interpreted to mean that the DNA is "double strand".*

Applicants respectfully disagree with the Examiner. Brennan et al. describe "short DNA oligomers can be both circularized (Ref. 14) and joined intermolecularly (Ref. 11)". Reference 14 and 11 are available in the footnotes of this document. Please note that the short DNA oligomers in Refs. 11 and 14 are "single strand DNA". Further, Brennan et al. describe, "We have found conditions under which 2'-deoxyribonucleoside 3' 5'-bisphosphate can be added to

DNA single strand DNA oligomers be joined in good yields (Refs. 15-18)". Please note again that the materials in Refs. 15-18 are all "single stranded DNA". Since Refs. 15, 16 and 18 describe "DNA oligomer" and Ref. 17 refers "single strand DNA oligonucleotide", Brennan et al. must be referring to only single strand DNA oligomers. There is no basis to assume the author also means double stranded DNA oligomers.

It has been well established for one of skill in the art that "DNA oligomer" should means "single strand DNA". For example, "oligomer" on Wikipedia indicates, "In biochemistry, the term oligomer is used for short, single stranded nucleic acid fragments such DNA or RNA, or similar fragments of analogs of nucleic acids such as peptide nucleic acid or Morpholinos."

In addition, the Examiner states in the Office Action that *Brennan et al teaches conditions for DNA joining reaction at page 44.* Applicants note that "DNA joining reaction" means an addition of one dT to DNA oligomer (Refs. 15-18). Even if the DNA oligomer would be double strand DNA, Brennan et al. may teach conditions for adding one dT to the double stranded DNA, not ligation of a double stranded DNA oligomer with another double stranded DNA oligomer.

Applicants therefore note that they have provided reasonable and persuasive evidence indicating that Brennan et al fails to teach that double stranded DNA can be circularized by T4 RNA ligase as claimed. The Examiner has asserted that Brennan can be reasonably read to indicate that T4 RNA ligase can be used to ligate double stranded DNA as claimed. However, there does not appear to be any basis in the references cited by the authors of Brennan et al. In fact, a reasonable reading of Brennan et al in light of such references as well as in light of the knowledge in the art clearly shows that DNA oligomers are single stranded and the cited process would not be expected to work. If the Examiner disagrees with Applicants reading of Brennan it is respectfully requested that the Examiner set forth evidence showing that DNA oligomers are understood by a person of skill in the art to include both single stranded and double stranded species.

The inventors have found that:

(1) in the case where the circularizing step (iii) of claim 1 was performed with T4 DNA ligase, clones having cDNA insert were not obtained, which means that DNA ligase does not function to ligate one end of double strand DNA with one end of mRNA/DNA heteroduplex; and

(2) no ligating reactions were occur when T4 RNA ligase was applied to a cleavage site of double stranded DNA vector, which means that T4 RNA ligase have no action for ligating both

ends of double strand DNA.

Applicants emphasize again that the circularizing step (iii) is performed with T4 RNA ligase, even though the inventors are not sure why T4 RNA ligase can ligate an end of double strand DNA primer to one end of mRNA/cDNA heteroduplex.

Thus, for the above noted reasons it is clear to a person of skill in the art that the claimed invention is not rendered obvious by the cited references as there is no teaching or suggestion in such references that T4 RNA ligase can ligate an end of double stranded DNA to an end of an mRNA/cDNA heteroduplex. Thus, these rejections are untenable and should be withdrawn.

CONCLUSION

In view of the foregoing amendments and remarks, it is respectfully submitted that the present application is in condition for allowance and early notice to that effect is hereby requested.

If the Examiner has any comments or proposals for expediting prosecution, please contact the undersigned attorney at the telephone number below.

Respectfully submitted,

Seishi KATO et al.

/William R. Schmidt, II/

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July 8, 2011